In this special issue

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EDITORIAL

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The second special issue of Histochem Cell Biol on single-molecule super-resolution microscopy covers various aspects of the application of this technique that have revolutionized the study of biological processes and structures at the nanoscale as pointed out in the Foreword by Jennifer Lipincott-Schwartz. The topic is surveyed in two "Review Articles" and in seven "Original Articles."

Hendrik Deschout, Aleksandra Radenovic, and their colleagues (Deschout et al. 2014) review recent progress in single-molecule resolution microscopy with emphasis on quantitative measurements such as counting of single molecules (i.e., NMDA receptors, glycine-gated channels, and asialo-glycoprotein receptor) with PALM, analysis of heterogeneity in the spatial organization of general membrane proteins or networks of signaling receptors and nuclear pore complexes, and single-molecule colocalization involving dual-color super-resolution microscopy to analyze, for example, protein–protein interactions. Both the potential of the technique and currently existing problems (i.e., limited detection efficiency, overcounting due to photoblinking, sample drift, localization uncertainty, and photoconversion efficiency of fluorescent proteins) using these tools are evaluated. Virgile Adam (2014) focuses on the different classes of phototransformable fluorescent proteins and the variable applications for which they are useful. These applications include not only the monitoring of cellular dynamics in *Drosophila* embryos, the tracking of cells and of cell division during the embryogenesis of zebrafish, in mice embryos, or brain as well as in plant tissues but also two-color pulse-chase-type imaging of molecules and mapping of proteins with photoacoustic and photothermal effects. With certain inherent limitations, the use of phototransformable fluorescent proteins for optical data storage has been shown to be feasible, and more realistic applications include ion, temperature, viscosity, and pH sensing.

Christoph Cremer and colleagues (Cremer et al. 2014) report original work performed with a special localization microscopy method and spectral precision distance/position determination microscopy (SPDM) and demonstrate its great advantages for the analysis of both viral pathogens as well as virus-derived nanotools. SPDM with the use of standard fluorescent dyes in the visible spectrum and standard microscopic preparation techniques permitted the analysis of the aggregation state of modified tobacco mosaic virus particles with an accuracy of better than 8 nm. Dynamic parameters of virus–cell attachment and infection by influenza A virus as well as of various infection-related membrane proteins were analyzed with high precision by SPDM nanoimaging. Four perspectives for nanoimaging by SPDM are enumerated: virus–cell membrane interaction; expression of viral genes; optimization of (plant-) virus-based nanotools and biodetection devices; and identification of viruses by oligonucleotide labeling. Related to this work are the studies by Patrick Müller and colleagues (Müller et al. 2014) on the spatial distribution and structural arrangement of a murine cytomegalovirus glycoprotein, gp36.5/m164, as detected by SPDM localization microscopy. They show that by next neighbor distance analyses, appropriate characterization parameters for cellular structures and structural arrangements of cellular molecules can also be obtained from pure pointillist localization microscopy

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images. Specifically, they were able to snapshot-like monitor the trafficking of the mCM-induced gp36.5/m164, and its spatial arrangements could be quantified with nanometer precision. Kristof Notelaers and colleagues (Notelaers et al. 2014) used *d*STORM to obtain super-resolution images of the membrane distribution of glycine receptor (GlyR) α3 splice variants α3K and α3L in order to investigate the role of RNA splicing in determining the GlyR distribution. By single- and dual-color imaging and pair correlation analysis to quantify the GlyR membrane distribution, both variants appeared to dynamically cluster via the same interactions, yet with strongly differing, splice-variant-dependent affinity. Franziska Fricke and colleagues (Fricke et al. 2014) applied super-resolution microscopy to obtain quantitative information on tumor necrosis factor receptor 1 (TNF-R1) cluster sizes and copy numbers before and after ligand binding. In the absence of ligand, TNF-R1 was present in dimers in the plasma membrane of HeLa cells. Following ligand binding, pre-assembled TNF-R1 dimers formed clusters of 3–6 receptors with clusters composed of more than four being favored, which would represent the signaling competent receptor complex. Laura Tarancón Diez and colleagues from Geneva and Frankfurt (Tarancón Diez et al. 2014) have quantitatively investigated the recruitment of arrestin3 to C–C chemokine receptor 5 using single-molecule localization microscopy and morphological cluster analysis after stimulation of the receptor with different anti-HIV analogues of the chemokine RANTES. They report that only classical agonists efficiently recruited arrestin3 to clusters larger than 150 nm in size, which suggests the existence of a link between arrestin3 recruitment to C–C chemokine receptors and G-protein activation. Stochastic super-resolution imaging methods rely on the localization of single emitters, which can involve the controlled photoswitching/activation of fluorescent proteins or synthetic dyes. Synthetic fluorophores with their small size can easily be chemically modified and used for stoichiometric labeling of proteins in live cells (van de Linde et al. 2012). Margot Schikora together with Subrata Dutta and Andriy Mokhir (Schikora et al. 2014) developed a simple, high-yield synthesis of conjugates of a deuterated dihydro *N*,*N*,*N*′,*N*′-tetramethylrhodamine (F*) with nuclease-resistant chemically modified oligonucleotide (2′-OMe RNA). They demonstrated that in the presence of a target nucleic acid and an appropriate photocatalyst, F* is oxidized to form a fluorescent F. The background reaction in the absence of a target nucleic acid took >30 times longer. Additionally, a single mismatch in the target nucleic acid reduced the templated reaction 8 times. Hence, these activatable synthetic dyes should find applications as nucleic acid-specific probes for super-resolution imaging in live cells. Marko Sustarsic, Achillefs Kapanidis, and colleagues (Sustarsic et al. 2014) worked out an optimized electroporation protocol for intracellular delivery of organically labeled proteins of up to 60 kDa in *E. coli*. The authors emphasize the potential of their electroporation protocol for in vivo single-cell and single-molecule FRET studies.

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